IN THE SPECIFICATION:

Please replace the second paragraph on page 24 with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

As used above, "integrin receptor antagonists" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the ~~□v□3~~ $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the ~~□v□5~~ $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the ~~□v□3~~ $\alpha_v\beta_3$ integrin and the ~~□v□5~~ $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the ~~□v□6, □v□8, □1□1, □2□1, □5□1, □6□1 and □6□4~~ $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of ~~□v□3, □v□5, □v□6, □v□8, □1□1, □2□1, □5□1, □6□1 and □6□4~~ $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. H.N. Lode and coworkers in PNAS USA 96: 1591-1596 (1999) have observed synergistic effects between an antiangiogenic ~~□v~~ αv integrin antagonist and a tumor-specific antibody-cytokine (interleukin-2) fusion protein in the eradication of spontaneous tumor metastases. Their results suggested this combination as having potential for the treatment of cancer and metastatic tumor growth. $\alpha_V\beta_3$ integrin receptor antagonists inhibit bone resorption through a new mechanism distinct from that of all currently available drugs. Integrins are heterodimeric transmembrane adhesion receptors that mediate cell-cell and cell-matrix interactions. The α and β integrin subunits interact non-covalently and bind extracellular matrix ligands in a divalent cation-dependent manner. The most abundant integrin on osteoclasts is $\alpha_V\beta_3$ ($>10^7$/osteoclast), which appears to play a rate-limiting role in cytoskeletal organization important for cell migration and polarization. The $\alpha_V\beta_3$ antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of macular degeneration, inhibition of arthritis, and inhibition of cancer and metastatic growth.

Please replace the third paragraph on page 25 with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

An "inhibitor of interleukin-1 beta" or ~~IL-1□~~ IL-1β refers to in inhibitors of IL-1, which is a soluble factor produced by monocytes, macrophages, and other cells which activates T-lymphocytes and potentiates their response to mitogens or antigens. Nonlimiting examples of IL-1B inhibitors include diacerein and rhein.

Please replace the first paragraph on page 34, after Scheme 2, with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

Compounds of the current invention may also be prepared according to Scheme 3. Thus, a suitably substituted cycloalkanone (such as R^3,R^4=F; Cl; *spiro*-cyclopropyl or CH_3; see Patrick, T. B.; Scheibel, J. J.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 3917-3918; Harmata, M.; Shao, L. *Synthesis* **1999**, 1534-1540; Crandall, J. K.; Seidewand, R. J. *J. Org. Chem.* **1970**, *35*, 697-701; or Negishi, E.; Chatterjee, S. *Tetrahedron Lett.* **1983**, *24*, 1341-1344, respectively) can be converted to the α,β unsaturated ketoester by treatment with a suitable base such as sodium hydride and subsequent quenching of the resulting enolate anion with dimethyl carbonate followed by oxidation with PhSeCl/pyr/H_2O_2. This compound can then serve as an electrophile in conjugate addition reactions with a variety of nucleophiles such as, but not limited to, bifunctional organocopper reagents. Reductive removal of the ketone functionality via the tosylhydrazone (see Taber, D. F; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717-3721), or alternatively by Raney nickel desulfurization of the corresponding thioacetal (see Newman, M. S.; Walborsky, H. M. *J. Am. Chem. Soc.*, **1950**, *72*, 4296-4297), followed by ester hydrolysis and peptide coupling as described in Scheme 2 yields compounds of the current invention. When X is a protected oxygen functionality, a Suzuki reaction (via the triflate) followed by ester hydrolysis and peptide coupling as described in Scheme 2 provides compounds of the current invention.

Please replace the first full paragraph on page 35, after Scheme 3, with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

A diverse array of compounds of the current invention where D is a heterocycle can be prepared as shown in Scheme 4. Copper mediated conjugate addition of a vinyl lithium or magnesium species to the α,β unsaturated ketoester from Scheme 3 followed by ketone removal as discussed for scheme 2 affords a versatile intermediate olefin (boxed) that can be selectively converted (when E=aryl or heteroaryl) to one of two regioisomeric ketones by subjecting it to either a rhodium catalyzed hydroboration (see Hayashi, T.; Matsumoto, Y. *Tetrahedron. Asymmetry* **1991**, *2*, 601-612 and references therein), oxidation sequence or alternatively a Wacker oxidation in one case or epoxidation followed by an acid catalyzed epoxide rearrangement (see Ranu, B. C.; Jana, U. *J. Org. Chem*, **1998**, *63*, 8212-16 and references therein) in the other. These ketones may also be interconverted through a carbonyl transposition sequence via the corresponding α phenylsulfenylketones (see Trost, B. M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc.*, **1975**, *97*, 438-440). Each of these α methylene-ketones can then be further transformed into a variety of heterocycles, such as thiazole, isothiazole, oxazole, isoxazole, triazole, imidazole, thiadizaole, etc., according to well established literature precedents (see Gauthier, J. Y. et al. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 87-92 and references therein). Ester hydrolysis and peptide coupling as per Scheme 1 yields compounds of the current invention.

Please replace the first paragraph on page 37, after Scheme 4, with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

Compounds of the current invention may also be prepared according to Scheme 5a. Addition of a vinyl (m=0) or allyl (m=1) Grignard reagent to the α,β -unsaturated ketoester from Scheme 3 in the presence of a suitable copper (I) catalyst affords the conjugate addition product. Reductive removal of the ketone and reaction with ozone leads to the corresponding aldehyde. The aldehyde derived from the conjugate addition of vinyl Grignard (m=0) to the α,β -unsaturated ketoester can be transformed into a terminal alkyne with CBr_4, PPh_3 and base. A Sonagashira reaction then gives another versatile intermediate (boxed) that can be utilized to prepare compounds of the current invention where D=alkene, alkyne or heterocycle as indicated. Alternatively, this intermediate can be accessed, as shown in Scheme 5b, through direct 1,4-addition of the alkyne fragment (see Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182-187) to the previously mentioned α,β -unsaturated ketoester from Scheme 3.

Please replace the first paragraph on page 39, after Scheme 5B, with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

Compounds of the current invention may also be prepared according to the chemistry outlined in Scheme 5c. Thus, Grignard addition to the homologous aldehyde intermediates (m=0, m=1), that were generated by ozonolysis of the corresponding terminal olefins in Scheme 5a, followed by oxidation of the resulting alcohol affords the regioisomeric α-methylene ketones and subsequently compounds of the current invention according to Scheme 4.

Please replace the first paragraph on page 40, after Scheme 5C, with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

Compounds of the current invention may also be prepared according to Scheme 6. Cyclohept-4-en-1-one (Louis, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312-11313) can be converted into a variety of *gem*-disubstituted derivatives according to the discussion accompanying Scheme 2 and further to the terminally differentiated aldehyde-ester by Schreiber ozonolysis (Schreiber, S. L.; Claus, R. E.; Reagen, J. *Tetrahedron Lett.* **1982**, *23*, 3867-3870). Sequential Horner-Wadsworth-Emmons type olefination, with an appropriate α-phosphonylketone, and intramolecular 1,4-addition leads to an α-methylene ketone that can be transformed into compounds of the current invention according to Scheme 4.

Please replace the first paragraph on page 41, after Scheme 6, with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

Compounds of the current invention may also be prepared according to Scheme 7. Wittig reaction of a variety of aldehydes with ethoxy(ethoxycarbonyl)methyl) triphenylphosponium chloride yields α-ketoacid derivatives after hydrolysis of the enol-ether and ester functionalities (see Bach, K. K.; El-Seedi, H. R.; Jensen, H. M.; Nielsen, H. B.; Thomsen, I.; Torssell, K. B. G. *Tetrahedron* **1994**, *50*, 7543-7556). A Robinson-annelation/reduction sequence (see Ziegler, F. E.; Condon, M. E. *J. Org. Chem.* **1971**, *36*, 3707-3713) then affords a cyclohexanone intermediate that can be transformed into compounds of the current invention according to Scheme 2.

Please replace the first paragraph on page 42, after Scheme 7, with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

Compounds of the current invention may also be prepared according to Scheme 8. Thus, treatment of the known α,β-unsaturated ketoester (see Webster, F. X.; Silverstein, R. M. *Synthesis* **1987**, 922-924) with DAST or alternatively with PCl_5 affords the corresponding *gem*-difluroro (R^3, R^4=F) and *gem*-dichloro (R^3, R^4=F) compounds respectively. A reduction/oxidation sequence affords the α,β-unsaturated aldehyde from the ester. Iminium ion catalyzed Mukaiyama-Michael addition (see Brown, S. P.; Goodwin, N. C.; Macmillan D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192-94) of a methylketone-derived enol-silyl ether, oxidation of the aldehyde to an acid and esterification with diazomethane yields a keto-ester that can be converted into compounds of the current invention according to Scheme 4. It will be appreciated by those skilled in the art of organic synthesis that the α,β-unsaturated aldehyde intermediate (boxed) in Scheme 8 can also be converted to compounds of the current invention according to the conjugate addition strategies detailed in Schemes 3 through 5a-c; this facet is illustrated in Scheme 9 (note analogy to Scheme 5b).

Please replace the first paragraph on page 45 with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

Bromotrimethylsilane (1.96 mL, 15.1 mmol) was added dropwise to a 0°C solution of dimethyl sulfoxide (1.10 mL, 15.5 mmol) in chloroform (15 mL) with stirring at this temperature for 30 minutes. (–)-(1*R*,6*R*)-6-(2-bromophenyl)cyclohex-3-ene-1-carboxylic acid (4.24 g, 15.1 mmol; prepared in 93% *ee*, $[\alpha]_D = -62°$ (c=1.0, $CHCl_3$), by resolution of the racemic Diels-Alder adduct between 1,3-butadiene and 2-bromocinnamic acid [see Morin, R.; Manuel, C.; Mazmanian, C. *Eur. J. Med. Chem.* **1976**, *11*, 493-499] with (*R*)-phenethyl amine) was added as a solid with stirring at rt for 1 h prior to the addition of diisopropylethylamine (2.65 mL, 15.2 mmol) at 0°C followed by reflux for 24 hours. The reaction vessel contents were then cooled to rt, diluted with ethyl acetate and washed in succession with water, 5% HCl, water and brine, and the organic phase was dried over sodium

sulfate. Concentration in vacuo afforded (1*R*,2*R*,4*R*,5*S*)-4-bromo-2-(2-bromophenyl)-6-oxabicyclo[3.2.1] octan-7-one as an oily solid.

Please replace the fifth paragraph on page 45 with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

A stirred solution of methyl (1*R*,2*R*)-2-(2-bromophenyl)-5-oxocyclohexanecarboxylate (1.69 g, 5.46 mmol) in CH_2Cl_2 (23 mL) was treated at –20°C with methanol (22 ~~μ~~μL, 10 mol%) and diethylaminosulfur trifluoride (DAST) (1.73 mL, 13.1 mmol) with slow warming to room temperature over 1.5 hours and additional stirring at room temperature for 30 minutes. Excess reagent was quenched by the careful addition of saturated sodium bicarbonate solution at 0°C. The reaction vessel contents were then diluted with dichloromethane and washed with saturated sodium bicarbonate aqueous solution and water, and dried (Na_2SO_4). Concentration *in vacuo* gave methyl (1*R*,2*R*)-2-(2-bromophenyl)-5,5-difluorocyclohexanecarboxylate as a thick, brown syrup.

Please replace the second paragraph on page 47 with the paragraph provided below (strikethrough and underlining are used to highlight the changes):

(1*R*,2*R*)-2-(2-Bromophenyl)-*N*-(1-cyanocyclopropyl)-5,5-difluorocyclohexanecarboxamide (518 mg, 1.35 mmol), 4-(methylthio) benzeneboronic acid (285 mg, 1.70 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (61 mg, 0.075 mmol) and 2.0 M Na_2CO_3 aqueous solution (1.02 mL, 2.04 mmol) were heated at 85°C in *N, N*-dimethylformamide (4.0 mL) under a nitrogen atmosphere. After 17 hours at this temperature, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water and the layers separated. The aqueous phase was extracted with additional ethyl acetate and the combined organics were washed with brine, and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue on silica eluting with 30/70 EtOAc/hexanes gave the title compound as a faint-yellow foam, $[\alpha]_D = -41°$ (c = 0.95, $CHCl_3$), MS (-ESI): 425.3 $[M-H]^-$.